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Value of estetrol determinations in the management of intrauterine growth retardation. Comparison with free estriol

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In recent years, various biochemical investigation techniques, e.g. determination of total estrogens in 24-hour urine, of unconjugated estriol (E_3), HPL and other placental steroids in the serum have been applied to a large scale to monitor feto-placental or placental function [2, 6, 11, 12, 20]. **However, up to the present no single parameter has proved to be the method of choice**, probably due to the fact that complex enzymatic systems or various organs are involved in the synthesis of steroid or protein hormones.

Estetrol (15α-estriol, E_4) **is a specific product of fetal metabolism.** The last synthetic steps depend on the hydroxylation capacity of the fetal liver. Important precursors of E_4 synthesis are estradiol-17β and to a smaller extent neutral C19 steroids of the fetoplacental unit [16, 18, 21]. From the fetus, the hormone passes into the maternal circulation and is mainly excreted as E_4-glucuronide in the urine [3].

First investigations in the urine and later also in the blood have shown that this steroid can be regarded as a good indicator of the fetal state in intrauterine danger [5, 9, 19]. By obtaining specific antisera to E_4, it has become possible in recent years to determine the low concentration of this steroid in the serum radioimmunologically without time consuming and technically elaborate separation methods [1, 4, 8, 16, 22]. The objective of the present investigation therefore is to establish in a larger group of patients whether the determination of unconjugated E_4 is superior to the measurement of other steroids especially in intrauterine growth retardation, since the significance of hormone assays is chiefly in the diagnosis of intrauterine growth disorders, and can thereby lead to an improvement of the detection of fetal danger states.

Curriculum vitae

HANS JÜRGEN KÜNZIG *was born 1940 in Düsseldorf. He studied medicine at the University of Freiburg and München. After graduation he worked for one year in the institute of pathology at the University of Köln. Since 1971 he has been on the staff of the Department of Obstetrics and Gynecology at the University of Köln. He qualified as a lecturer in Obstetrics and Gynecology in 1978. His fields of interest include the physiopathology of the feto-placental unit, poor intrauterine fetal growth, fetal distress and methods of detection.*

1 Materials and methods

1.1 Assay methods

The concentration of unconjugated serum E_4 is determined radioimmunologically with some mod-

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ifications as described by KÜNZIG and GEIGER for E_3 [10, 11]. The antiestetrol antiserum was kindly provided by Dr. P. G. D. DEAN [16]. The cross-reaction against E_3 is 0.4%, and against all other steroids less than 0.1%.

The method can be described briefly as follows: 0.5 ml of serum are extracted mechanically with 10 ml diethylether for 10 minutes. The tubes are then placed in a methanol bath (- 25 °C). After freezing the aqueous phase, the ether is poured into glass test tubes and evaporated with nitrogen. The residue is dissolved with 0.3 ml of ethanol and 2 X 0.1 ml transferred into disposable glass test tubes. The alcohol is evaporated once more and 0.1 ml 2.4–^{3}H-E_4 (specific activity 49 Ci/mM (NEN), 2 X 10^{-9} Mol), as well as 0.2 ml γ-globulin (5 mg/ml) and 0.2 ml anti-E_4 antiserum (1:14,000) are added (dissolved in phosphate-buffered saline). The test mixtures are incubated for 30 minutes at room temperature and at 4 °C, respectively. The antibody-bound and free steroid is separated by addition of 0.5 ml of a charcoal-dextran mixture with subsequent centrifugation. Afterwards, the antibody-bound radioactivity present in the supernatant is measured in a liquid-scintillation counter and the hormone concentration determined with reference to a standard curve. The calculation is performed with the aid of a computer program by means of spline approximation (Fa. BERTHOLD).

The recovery of unlabeled steroids, added to steroid free serum, is 91.9% (n = 22). The intra-assay variation is 8.4% (n = 10) and the interassay precision is 14.8% (n = 10). The lower limit of sensitivity of the standard curve is 20 pg E_4.

1.2 Patients investigated

1.2.1

The reference range for E_4 is determined by 279 determinations between the 22nd and 40th week of pregnancy. The samples derive from different outpatients and inpatients in a random sequence. Any pathology of pregnancy has been excluded.

1.2.2

To determine the variability of the serum level of E_4, blood was taken from three patients over four hours at an interval of 15 minutes and over 24 hours at an interval of 60 minutes, in 22 patients over 24 hours at an interval of four hours, as well as in four patients on five or six consecutive days.

1.2.3

In five patients, the serum E_4 level is determined before, during and after application of betamethasone (8, 8, 4, 4 mg on four consecutive days), in seven patients who had received an intravenous tocolysis with beta-sympathomimetics, as well as in six patients before and up to four days after commencement of a therapy with ampicillin.

1.2.4

A group of 151 patients delivered of babies with signs of intrauterine growth retardation was also investigated. The neonates were subdivided into "small for dates" below the 25th percentile and "very small for dates" below the 10th percentile according to LUBCHENKO [13], as well as into neonates with and without signs of dystrophy. The 25th and 10th percentile of the weightcharts of LUBCHENKO are comparable to the 10th and 3rd percentile of the weightcharts of NICKL [2]. Twenty-two and 24 highly retarded eutrophic and dystrophic babies (very small for dates) respectively as well as 75 and 24 slightly retarded eutrophic and dystrophic neonates (small for dates) respectively are found. For 55 of the 151 patients, three and more values are between the 30th and 40th week of pregnancy, so that an observation on the concentration course of E_4 is possible. This is made on the basis of the following criteria:

1.2.4.1

E_4 concentration primarily below the normal range.

1.2.4.2

Decrease of the E_4 level by more than 35% within the last two weeks of pregnancy.

1.2.4.3

Rising concentration, i.e. corresponding to normal.

The results are compared with the values of the unconjugated E_3 determined according to the method of KÜNZIG and GEIGER [10, 12].

2 Results

The serum level of unconjugated E_4 is 0.27 ± 0.06 ng/ml in the 22nd week of pregnancy and rises to 1.37 ± 0.65 ng/ml towards the end of pregnancy. However, **a sharper rise of the values only occurs from about the 30th week of pregnancy**. There is an appreciable variation of the individual values (n = 279) of the various patients around the mean value (Fig. 1).

The variability of the serum concentrations of E_4 is investigated by blood samples taken at 15 minute to 24 hour intervals (see methods). **The mean coefficient of variation is a minimum of 11.7 ± 4.3% and a maximum of 16.3 ± 9.5%** (Tab. I). It does not differ significantly from the precision within or between the series. **A diurnal rhythm cannot be demonstrated** over a period of 24 hours; only an undulating fluctuation is detectible. (Fig. 2).

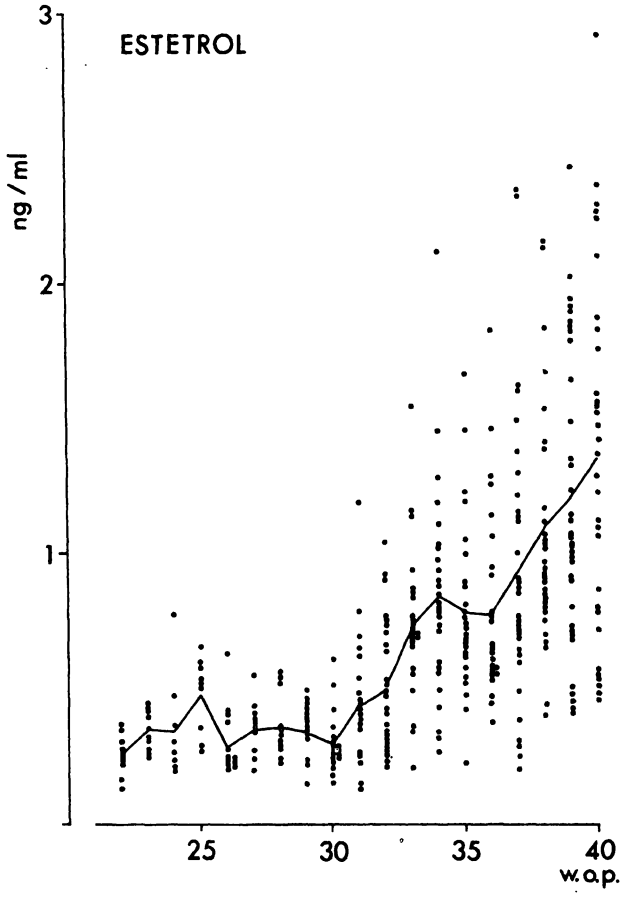

Fig. 1. Serum concentration of unconjugated estetrol. Individual levels (n = 279) and mean values between the 22nd and 40th week of pregnancy are shown.

Tab. I. Fluctuations of unconjugated estetrol.

No. of patients	observation time	interval of blood-sampling	coefficient of variation Mean ± S.D.
3	4 hrs	15′	11.7 ± 4.3
3	24 hrs	1 h	13.4 ± 2.5
22	24 hrs	4 h	14.5 ± 5.5
4	6 days	24 h	16.2 ± 9.5

Drugs such as corticosteroids, β-sympathomimetics or antibiotics show a distinct influence on the serum E_4 concentration. Within a few hours, there is a decline by an average of 30% compared to the mean initial concentration. With continuation of therapy, the initial value is regained after two to three days with β-sympathomimetics and after five days with ampicillin, whereas a fresh rise of the values can only be observed after discontinuation of the treatment with corticosteroids (Tab. II).

With intrauterine growth retardation below the 10th percentile, the E_4 concentration in the serum displays a characteristic course. As can be seen from Fig. 3b, no appreciable alteration of the values can be detected especially in the last five weeks of pregnancy, in which there is normally a rise of serum E_4 values. At the end of pregnancy, the mean value for "very small for dates" (n = 30) with signs of dystrophy is 0.93 ng/ml. For children of the same size without signs of dystrophy (n = 22), it is 0.86 ng/ml, corresponding to 60–70% of the normal. A similar course can also be recognized in "small for dates" with signs of dystrophy (n = 24) (Fig. 3a). The mean value at the end of pregnancy is 0.83 ng/ml and is thus about 40% below the normal for this stage of pregnancy. On the other hand, the serum level in "small for dates" without signs of dystrophy (n = 75) approximates more to the region of the normal curve and at the end of pregnancy a concentration of 1.20 ng/ml can be detected, i.e. the curve of the mean values practically corresponds to that of babies which have developed normally (Fig. 3a).

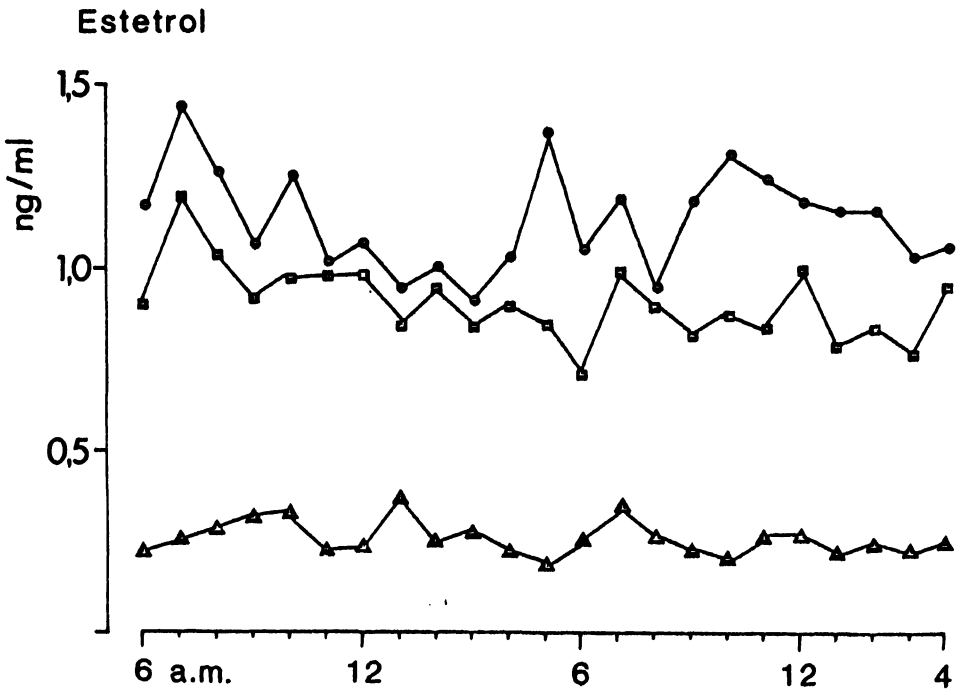

Fig. 2. Fluctuations of free estetrol over a 24 hour period in three patients.

Tab. II. Serum concentration of E_4 in percent of initial values under the influence of various drugs.

	hours after commencement of therapy							
	2	4	8	24	48	72	96	120
Betamethasone (n = 5)	-	-	-	79 ± 12	69 ± 16	75 ± 15	77 ± 15	83 ± 15
β-Sympathomimetics (n = 7)	91 ± 3	78 ± 9	77 ± 12	90 ± 13	88 ± 26	106 ± 49	-	-
Ampicillin (n = 6)	-	84 ± 13	-	73 ± 13	64 ± 6	80 ± 9	96 ± 6	99 ± 2

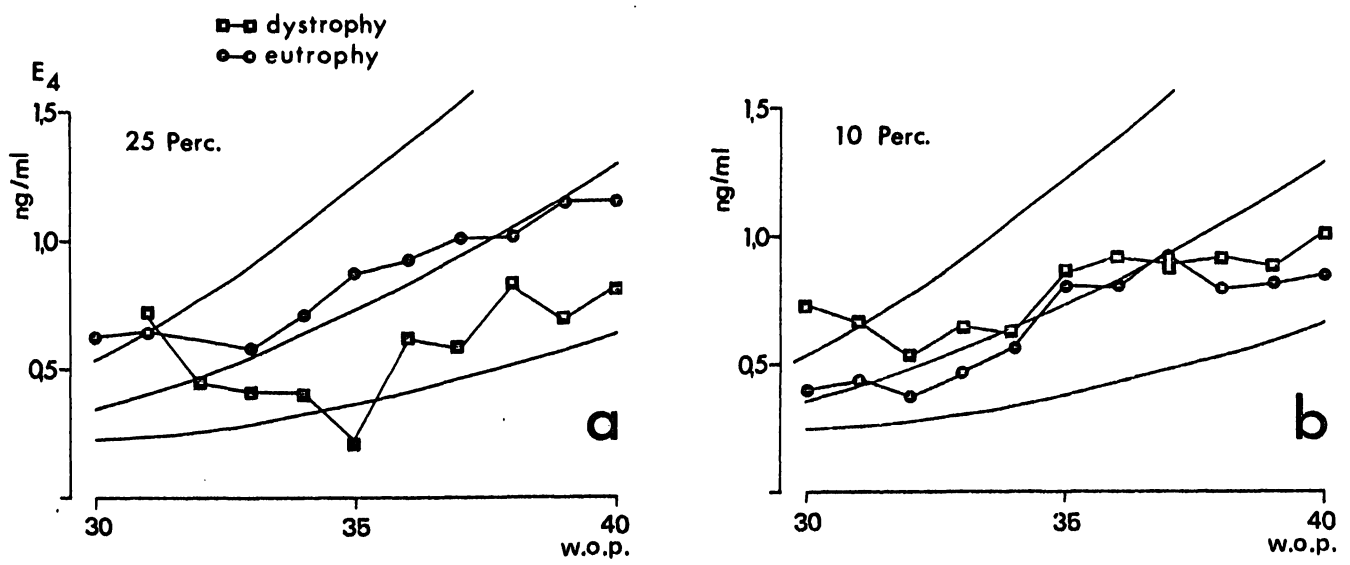

Fig. 3. Serum concentrations of unconjugated estetrol (mean values) in intrauterine growth retardation below
a.) the 25th
b.) the 10th percentile of LUBCHENKO et al. [14]. The solid lines represent the 90th, 50th, and 10th percentile in normal pregnancy.

However, mean values can only indicate a tendency and for recognition of the diagnostic value of a method it appears meaningful to register the concentration course of individual patients. As can be seen from Table 3, **in "very small for dates" with signs of dystrophy pathological courses are present in 70% and in those without signs of dystrophy in 86%.** Slightly retarded dystrophic babies frequently also display pathological values (in 66%), whereas eutrophic neonates of the same size reveal normal E_4 levels in 84%.

A comparison of the measurement of the well established method of free E_3 compared to E_4 in routine clinical tests shows that pathological E_4 or E_3 values can be detected in eight out of 31 or eight out of 29 "small for dates" respectively. On the other hand, in severe retardation pathological E_4 or E_3 values can be detected in 18 and 17 out 24 babies (Tab. III). A normal concentration of the two hormones can be detected only in three cases out of the "very small for dates", so that in this group there is suspicion of an intrauterine growth retardation in 88% of the cases of this group on the basis of the measurement of both hormones. As a whole, **a divergent course of the two hormones can nevertheless be detected in 13 out of 53 cases (25%) (Tab. IV).**

Tab. III. Serial serum E_4 and E_3 levels in intrauterine growth retardation.

	VERY SMALL FOR DATES						SMALL FOR DATES					
	Dystrophy		Eutrophy		Σ		Dystrophy		Eutrophy		Σ	
	E_4	E_3	E_4	E_3	E_4	E_3	E_4	E_3	E_4	E_3	E_4	E_3
No. of patients	17	17	7	7	24	24	6	4	25	25	31	29
below normal	7 (41%)	8 (47%)	4 (57%)	4 (57%)	11 (46%)	12 (50%)	2 (33%)	-	3 (12%)	5 (20%)	5 (16%)	5 (17%)
decrease > 35%	5 (29%)	5 (29%)	2 (29%)	-	7 (29%)	5 (21%)	2 (33%)	-	1 (4%)	3 (12%)	3 (10%)	3 (10%)
suspicious values	12 (70%)	13 (76%)	6 (86%)	4 (57%)	18 (75%)	17 (71%)	4 (66%)	-	4 (16%)	8 (32%)	8 (26%)	8 (27%)

Tab. IV. Serial serum E_4 levels in comparison to the concentration course of E_3 in intrauterine growth retardation.

	VERY SMALL FOR DATES			SMALL FOR DATES		
	Dystrophy	Eutrophy	Σ	Dystrophy	Eutrophy	Σ
No. of patients	17	7	24	4	25	29
Suspicious values E_4 + E_3	10 (59%)	4 (57%)	14 (58%)	-	4 (17%)	4 (14%)
Suspicious values E_4 + regular values E_3	2 (12%)	2 (29%)	4 (17%)	2 (50%)	-	2 (7%)
Suspicious values E_3 + regular values E_4	3 (18%)	-	3 (12%)	-	4 (16%)	4 (14%)
Regular values E_4 + E_3	2 (12%)	1 (14%)	3 (12%)	2 (50%)	17 (68%)	19 (66%)

3 Discussion

Our results show that with specific antisera to E_4, the radioimmunological determination of this steroid can be used as a routine method for surveillance of risk pregnancies.

From the 22nd to the 30th week of pregnancy, the serum level of E_4 practically does not change with values between 0.24 and 0.37 ng/ml. Then a rise follows, which is intensified once again after the 36th week of pregnancy (surge point) up to the end of pregnancy [9]. Here, the mean value is 1.37 ng/ml. Our values are in accordance with those of other authors [1, 9, 18, 21] who likewise use specific antisera. Only KORDA [7] reports extremely high concentrations around 5 ng/ml at the end of pregnancy; these must be regarded as methodological in origin.

Even with more frequent blood samples, we were unable to detect a diurnal rhythm as was already suspected by TULCHINSKY et al. [19] as well as NOTATION and TAGATZ [15]. Only uncharacteristic fluctuations with a mean coefficient of variation between 11.7 and 14.5% are found. The day-to-day fluctuations (16.3%) are also in a similar range. They thus do not differ significantly from the precision in the series and between the series. Thus the variations of E_4 correspond over short and long time intervals to those of other estrogens and peptides in maternal blood [2, 11]. The daily fluctuations of NOTATION and TAGATZ [15] with in some cases 70% appear inexplicably high; however, an assay method with an unspecific antiserum as well as chromatographic separation was employed.

After application of drugs as corticosteroids, β-sympathomimetics or antibiotics (frequently administered in pathological pregnancies), **there is a rapid decrease of E_4 concentrations of about 30%**, although the values can rise again already under administration of the two latter drugs. These findings correspond to the results already obtained for E_3 on a large scale and appear to be due to comparable pathomechanisms [11]. From this there result important consequences for the interpretation of the hormone determination in the hospital during treatment with the substances specified above: the absence of a fresh rise or a continuous decrease of the E_4 concentration is not due to therapy, but must be regarded as a sign of deterioration of fetoplacental function.

Since the significance of hormone assays is chiefly in the diagnosis of intrauterine growth disorders, the value of the measurement of E_4 is depicted in the diagnosis of intrauterine growth retardation and the fetal danger states associated with this. In "small for dates" and "very small for dates" with signs of dystrophy, in particular the rise normally taking place in the last weeks of pregnancy cannot be detected and at the end of pregnancy the values are only about 60–70% of those of the normal group (Fig. 3a + b). In contrast to this, the serum concentration in eutrophic "small for dates" is very much nearer to the normal curve, since these involve genetically small babies without appreciable signs of an intrauterine growth disorder (Fig. 3a).

However, **single values can be regarded only as a "screening test" and a reliable evaluation of the fetoplacental unit is only possible on the basis of serial determinations.** Here it is shown that primarily pathological values (< 10th percentile) or a significant decrease of the concentration (> 35%) within the last two weeks of pregnancy indicate a fetal retardation or an acute deterioration of fetoplacental function. This applies to 75% of the "very small for dates" with and without signs of dystrophy (Tab. III).

A significant decrease of the E_4 level was also observed by TULCHINSKY et al. [19] in seven patients with severe pre-eclampsia and subsequent fetal death, whereas KUNDU et al. [9] assert a superiority to E_4 compared to determination of E_3 and HPL on the basis of comparative sequential observations. The results of NOTATION and TANGATZ [15] appear to us and also to other authors [9] to be difficult to interpret already for methodological reasons. Our comparative serial investigations of the assay of E_4 and E_3 in a group of 53 pregnancies with fetal retardation show that the number of suspicious curves of E_4 and E_3 in intrauterine growth retardation is roughly the same and thus the information conveyed is similar (Tab. III). However, only 14 out of 24 highly retarded babies display pathological courses of both steroids whereas in a further seven neonates of the same group only one hormone appears to be suspicious. **Thus a**

severe intrauterine growth retardation could be detected with a joint determination in 88% compared to 75% and 71% respectively when E_4 or E_3 was measured alone.
Determination of E_4 alone thus does not provide a fundamentally new possibility of prenatal diagnosis of intrauterine growth disorders. However, E_4 appears to be a further diagnostic adjunct similar to E_3 to a certain extent, and use of which can provide a further improvement of our diagnosis. The precondition for this is a further simplification of the laboratory methods, so that after automated determination the joint consideration of various diagnostic methods (similar to internal medicine) enables an early and certain appraisal of the fetal state.

Summary

Within recent years various biochemical tests have been used extensively for assessing the placental and the feto-placental function. However, at present, no single hormone assay seems entirely adequate for this purpose, since complex enzymatic systems and different organs are involved in the production of steroid and peptide hormones. Estetrol is considered to be a specific product of the fetal liver. With the recent availability of specific antisera to estetrol it has become possible to measure the small quantities of this steroid by radioimmunoassay without the requirement for prior chromatographic separation steps. Thereby the determination of estetrol can be used as a routine method on a large scale in high risk pregnancies. **In this study we investigated, whether the measurement of this steroid may improve the surveillance of risk pregnancies,** especially those complicated by intrauterine growth retardation and thereby contribute to the solution of some of the still unsolved problems.

The serum concentration of unconjugated estetrol increases from 0,27 ng/ml in the 22nd week of pregnancy to 1,37 ng/ml at term. However, mean values only start to rise more rapidly after the 30th week of gestation. The results of serial determinations at 15 min. to 24 hour intervals show slight fluctuations with no consistent pattern, the mean coefficients of variation being minimal 11,7%, maximal 16,3%. No diurnal variation is apparent. Corticosteroids, β-mimetic drugs and antibiotics cause an immidiate drop of the estetrol concentrations to about 70% of the initial values. Therefore estetrol exhibits a similar behavior to that of estriol under the influence of various drugs especially used in risk pregnancies and this has to be taken into account in hormonal monitoring.

The most marked changes in the concentration of estetrol are seen in intrauterine growth retardation. It can be observed that especially in very small for dates with and without signs of dystrophy the physiological rise in the last weeks of pregnancy is absent and the curve remains flat. At the end of gestation, mean values average 60–70% of the levels in regular pregnancy. The same trend applies to less retarded children also having signs of dystrophy. Serial determinations in 55 cases complicated by intrauterine growth retardation demonstrate, that 70% and 86% of very small for dates with and without signs of dystrophy show a suspicious hormonal pattern. Similar figures (66%) are seen in less retarded children with signs of dystrophy, too. On the contrary, **in slightly retarded eutrophic babies, regular levels can be depicted in 84%.** Comparing results of estetrol and estriol determinations show, that **the two estrogens give a similar information of the fetal state.** However, in 25% the hormone profiles may differ. **By joint determination of both steroids, suspicious values are depicted in 88% to 70–75% by single measurement of either hormone.** Therefore the determination of estetrol can not replace other biochemical tests of feto-placental function but is an additional adjunct in the detection of intrauterine growth-retardation. It enables further improvement of the antenatal diagnosis of this complication of pregnancy.

Keywords: Drugs, estetrol, estriol, fluctuations, intrauterine growth retardation, normal pregnancy, radioimmunoassay.

Zusammenfassung

Wertigkeit der Bestimmung von Östetrol bei der Diagnostik der intrauterinen Mangelentwicklung.
Vergleich mit unkojungiertem Östriol.

In den letzten Jahren sind verschiedene biochemische Untersuchungsverfahren in großem Umfang zur Überwachung der placentaren bzw. fetoplacentaren Funktion angewandt worden. Allerdings hat sich bis zum gegenwärtigen Zeitpunkt kein einzelner dieser Parameter als die Methode der Wahl erwiesen, da komplexe enzymatische Systeme oder verschiedene Organe an der Synthese von Steroiden und Peptiden beteiligt sind. Östetrol ist ein spezifisches Produkt des fetalen Leberstoffwechsels. Die Gewinnung spezifischer Antiseren gegen Östetrol hat es ermöglicht, die niedrige Konzentration dieses Steroids im Blut unter Auslassung zeitraubender und technisch aufwendiger Trennungsmethoden radioimmunologisch zu bestimmen. Hierdurch kann die Messung dieses Steroids als Routinemethode für die Überwachung von Risikoschwangerschaften herangezogen werden. **In der vorliegenden Arbeit wird geprüft, ob die Bestimmung des freien Östetrol im Blut zu einer Verbesserung der bisherigen antenatalen Diagnostik speziell der intrauterinen Mangelentwicklung beitragen kann.**

Der Serumspiegel des freien Östetrol steigt bei einem unausgewählten Patientengut von 0,27 ng/ml in der 22. Schwangerschaftswoche auf 1,37 ng/ml am Ende der Gra-

vidität an. Dabei erfolgt der Konzentrationsanstieg vorwiegend innerhalb der letzten 10 Schwangerschaftswochen. Bei Messung des Östetrolspiegels in 15 min. bis 24 std. Abständen finden sich unspezifische Fluktuationen mit mittleren Variationskoeffizienten von minimal 11,7%, maximal 16,3%; ein diurnaler Rhythmus kann nicht nachgewiesen werden. Medikamente wie Kortikosteroide, β-Sympatomimetika oder Antibiotika führen innerhalb weniger Stunden zu einem Absinken der Östetrolkonzentration von durchschnittlich 30% und lassen damit ein dem Östriol ähnliches Verhalten erkennen. Dies muß bei der hormonellen Überwachung in Betracht gezogen werden.

Bei intrauteriner Mangelentwicklung weist die E_4-Konzentration einen charakteristischen Verlauf auf. Der besonders in den letzten Schwangerschaftswochen erfolgende Anstieg ist nicht feststellbar und am Ende der Tragzeit entspricht der Mittelwert sowohl bei stark retardierten Kindern mit und ohne Dystrophiezeichen als auch bei leicht retardierten dystrophen Neugeborenen 60–70% der Norm. Retrospektive Verlaufsuntersuchungen von 55 Schwangerschaften mit intrauterinen Wachstumsstörungen zeigen: **Bei schwerer Retardierung** mit und ohne Dystrophiezeichen **liegen in 70% bzw. 86% pathologische Verläufe vor**, mit 66% weisen auch leicht retardierte dystrophe Kinder häufig suspekte Werte auf. **Dagegen lassen nur gering retardierte eutrophe Neugeborene in 84% normale Steroidspiegel erkennen.** Ein Vergleich der in der klinischen Routine erprobten Messung des freien Östriol gegenüber Östetrol läßt erkennen, daß die **Aussagefähigkeit von Östriol und Östetrol ähnlich** ist. Allerdings kann in 25% ein divergenter Verlauf vorliegen. **Durch gemeinsame Bestimmung beider Steroide läßt sich ein suspekter Verlauf bei schwerer Retardierung in 88% feststellen gegenüber 70–75% bei alleiniger Messung eines der Hormone.** Somit ersetzt die Messung von Östetrol nicht die der bisher erprobten biochemischen Parameter sondern scheint ein zusätzlicher Mosaikstein in der Diagnostik intrauteriner Wachstumsstörungen zu sein, der in Verbindung mit diesen zu einer weiteren Verbesserung der antenatalen Diagnostik beitragen kann.

Schlüsselwörter: Fluktuationen, intrauterine Mangelentwicklung, Medikamente, normale Schwangerschaft, Östetrol, Östriol, Radioimmunoassay.

Résumé

La valeur de l'estimation de oestetrol pour le diagnostic de la défience de croissance intra-utérine.
Comparée avec l'oestriol non-conjugé.

Durant ces dernières années de différentes méthodes biochimiques fûrent appliquées à grande échelle pour la surveillance de la fonction placentaire où la fonction foetoplacentaire. Jusqu'à présent aucun de ces paramètres ne pouvait étre considéré comme la meilleure, parce que des systèmes enzymatiques complexes ou des organes différents sont responsables de la synthèse des stéroides et des peptides. L'oestetrol est un produit spécifique du métabolisme hépatique foetal. L'extraction d'un anti-serum spécifique d'oestetrol a permis de mesurer par méthode radioimmunologique une concentration minime dans le sang, en évitant des méthodes de séparation compliquées. Donc la mesure de ce stéroid peut être utilisée comme méthode de routine pour la surveillance de grossesses à haut risque.

Dans ce travail-ci on a examiné si l'estimation d'oestetrol-libre dans le sang pouvait être une amélioration du diagnostic antenatal contemporain, spécialement pour le cas de défience de croissance intra-uterine. Le taux le serum d'oestetrol-libre monte de 0,27 ng/ml au moment de la 22me semaine de grossesse jusqu'à 1,37 ng/ml à la fin de la grossesse, mesuré dans un lot de patients pris au hasard. De là il s'ensuit que la montée de la concentration se produit surtout durant les 10 dernières semaines. Par la mesure de taux d'oestetrol dans un délai de 15 min à 24 heures, on trouve des fluctuations nonspécifiques avec un coefficient de variation moyen d'un minimum de 11,7% et comme maximum 6,3%; un rythme diurne ne peut-être prouvé.

Des médicaments, comme les corticostéroides, les β-sympaticomimétiques ou les antibiotiques induisent endéans peu d'heures une chute de la concentration d'oestetrol d'une valeur moyenne de 30% et produisent un effet comparable à celui produit sur l'oestriol. On doit en tenir compte dans la surveillance hormonale. **Dans la déficience de croissance intra-utérine, la concentration d'E-4 montre un tracé caractéristique.** L'augmentation durant les dernières semaines de grossesse n'est pas retrouvée.

A la fin de la grossesse la valeur moyenne ne représente que 60–70% des normes chez les enfants fortement retardés avec ou sans signes de dystrophie ainsi que chez des nouveau-nés dystrophiques legèrement retardés.

La rétrospective des examens de 55 grossesses présentant des troubles de croissances intra-utérines, a montré: **dans les cas d'enfants gravement retardés** avec ou sans signes de dystrophie **il y avait de 71% à 86% de tracés pathologiques**, des enfants dystrophiques légèrement retardés avaient des valeurs suspectes dans 66% des cas.

Des nouveau-nés eutrophes légèrement retardés présentaient dans 84% des cas des taux de stéroides normaux. En comparant lors de mesures de routine en clinique, l'oestriol-libre avec l'oestetrol **on en déduit que l'oestriol et l'oestetrol donnent près que la même valeur clinique**, néanmoins on peut trouver dans 25% des cas une suite divergente. **Par la mesure des deux hormones on en arrive à une estimation de 88% des cas suspectes chez les retardés graves, contre 70–75% par le mesure d'une seule hormone.** L'estimation d'oestetrol ne remplace les paramètres biochimiques utilisés jusqu'à présent mais semble être un test supplémentaire dans le diagnostic des troubles de croissance intra-utérine en améliorant le diagnostic anténatal.

Mots-clés: fluctuations, troubles de croissance intra-utérine, médicaments, oestetrol, oestriol, grossesse normale, radioimmunoassay.

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